JC13 Rec'd PCT/PTO 17 JAN 2002

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
29342/36230A	10/031464

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/11130	26 April 2000	03 August 1999

TITLE OF INVENTION

BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US

OREN, Peter L.; ANDERSON, Neil R.; KRAL, Martha A.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☒ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Return receipt postcard

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031464	PCT/US00/11130	29342/36230A

24. The following fees are submitted:.	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $740.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	26 - 20 =	6	x $18.00	$108.00	
Independent claims	1 - 3 =	0	x $84.00	$0.00	
Multiple Dependent Claims **(check if applicable).**			☐	$0.00	

TOTAL OF ABOVE CALCULATIONS =	$998.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00	
SUBTOTAL =	$998.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00	
TOTAL NATIONAL FEE =	$998.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	$0.00	
TOTAL FEES ENCLOSED =	$998.00	
Amount to be: refunded	$	
charged	$	

a. ☒ A check in the amount of **$998.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-2855** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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James J. Napoli
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32,361
REGISTRATION NUMBER

17 January 2002
DATE

10/031464
JC13 Rec'd PCT/PTO 17 JAN 2002

#2/a

PATENT APPLICATION

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:	"EXPRESS MAIL" mailing label No. **EK657815976US**
PETER L. OREN ET AL.	
U.S. National Phase of International Application No. PCT/US00/11130 filed under 35 U.S.C. §371	Date of Deposit: **January 17, 2002**
International Filing Date: 26 April 2000	I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner of Patents, Washington, D.C. 20231.
Filed: Herewith	
For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**	
Group Art Unit: Unknown	
Examiner: Unknown	
Attorney Docket No. 29342/36230A	Richard Zimmermann

PRELIMINARY AMENDMENT ACCOMPANYING NEW APPLICATION TRANSMITTAL

Box PCT
Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application filed under 35 U.S.C. §371 as follows:

IN THE SPECIFICATION:

Page 1, after the title, please delete the CROSS-REFERENCE TO RELATED APPLICATION in its entirety and insert therefor:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11130, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/146,924, filed August 3, 1999.--

IN THE CLAIMS:

Cancel claim 27.

REMARKS

Claims 1-27 are pending in the application. Claim 27 has been cancelled by this amendment. Therefore, claims 1-26 are at issue.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the specification and claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

This preliminary amendment adds no new matter. The specification has been amended to insert a new cross reference to related applications. The claims have been amended to conform the claims to U.S. practice.

It is submitted that this amendment should be entered and that the claims are in proper form for examination. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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January 17, 2002

10/031464
JC13 Rec'd PCT/PTO 17 JAN 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE
(U.S. National Stage of PCT/US00/11130
filed January 17, 2002)

IN THE SPECIFICATION:

The following cross-reference to related application has been inserted into the specification:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11130, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/146,924, filed August 3, 1999.

IN THE CLAIMS:

Claim 27 has been cancelled without prejudice.

β-CARBOLINE PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional U.S. Patent Application Serial No. 60/146,924, filed August 3, 1999.

FIELD OF THE INVENTION

This invention relates to the fields of pharmaceutical and organic chemistry involving β-carboline compounds which are useful in the treatment of the various medical indications where inhibition of type 5 cGMP-specific phosphodiesterase is desired. More particularly, β-carboline compounds are formulated in a manner providing uniform potency, and desirable stability and bioavailability characteristics.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (A. Taher et al., *J. Urol.*, *149*, pp. 285A (1993)).

Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (K.J. Murray, *DN&P 6(3)*, pp. 150-56 (1993)).

Daugan U.S. Patent No. 5,859,006 discloses a class of β-carbolines, and pharmaceutical compositions thereof, which are useful in the treatment of conditions wherein inhibition of PDE5 is desired. Also, see PCT publication WO 97/03675 disclosing the use of such β-carbolines for the treatment of sexual dysfunction.

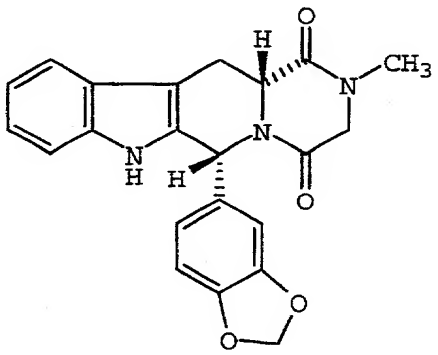
The poor solubility of many β-carbolines useful as PDE5 inhibitors has prompted the development of coprecipitate preparations, as disclosed in Butler U.S. Patent No. 5,985,326. Briefly described, coprecipitates of β-carbolines with a polymer, e.g., hydroxypropyl methylcellulose phthalate, were prepared, then milled, mixed with excipients, and compressed into tablets for oral administration. However, studies revealed some difficulties in generating precisely reproducible lots of coprecipitate product, thereby making the use of coprecipitates less than ideal for pharmaceutical formulations.

In addition, clinical studies involving administration of tablets containing such a coprecipitate preliminarily revealed that maximum blood concentration of the β-carboline is achieved in 3 to 4 hours, with the average time for onset of a therapeutic effect as yet not precisely determined. When used for the treatment of sexual dysfunction, such as male erectile dysfunction or female arousal disorder, a more rapid attainment of maximum blood concentration, along with a greater prospect for

rapid onset of therapeutic effect, is desired by patients, who prefer more immediate effects. Accordingly, there is a continuing need in the art for oral dosage forms of β-carbolines, and pharmaceutical compositions thereof, useful in the treatment of conditions where inhibition of PDE5 is beneficial.

SUMMARY OF THE INVENTION

This invention provides pharmaceutical formulations comprising a compound of structural formula (I):



(I)

named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and alternatively named (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione,

and pharmaceutically acceptable salts and solvates thereof, wherein the compound preferably is provided as a free drug,

in admixture with a diluent, a lubricant, a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof, a disintegrant selected from the group consisting of crospovidone, croscarmellose sodium, and a mixture thereof, and, optionally, microcrystalline cellulose and/or a wetting agent. Optionally, the formulation additionally comprises a second diluent.

A most preferred pharmaceutical formulation of the present invention comprises: (a) about 1 to about 5, and more preferably about 2 to about 4, weight percent of the compound of structural formula (I), provided as free drug; (b) about 50 to about 85 weight percent, and preferably about 50 to about 75 percent, lactose; (c) about 0.25 to about 2 weight percent magnesium stearate; (d) about 1 to about 5 weight percent hydroxypropylcellulose; (e) about 3 to about 15 weight percent croscarmellose sodium; (f) 0 to about 40 weight percent microcrystalline cellulose; and (g) 0 to about 5 weight percent sodium lauryl sulfate.

The present invention further relates to the use of such formulations for treatment of sexual dysfunction, e.g., male erectile dysfunction and female arousal disorder. The formulations can be administered orally as a compressed tablet or as dry, free-flowing particles encapsulated in a hard shell, for example, a gelatin shell.

DETAILED DESCRIPTION OF THE INVENTION

For purposes of the invention disclosed and claimed herein, the following terms and abbreviations have the following meanings.

The term "treatment" is defined to include preventing, lowering, stopping, or reversing the progression or severity of a condition or symptom being treated. As such, the present invention includes both medical therapeutic and/or prophylactic administration, as appropriate.

The term "effective amount" is an amount of a pharmaceutical formulation that is effective in treating the desired condition or symptom. An effective amount of the compound of structural formula (I) to treat sexual dysfunction in a male is an amount sufficient to provide and sustain an erection capable of penetrating his partner. An effective amount of the compound of structural formula (I) to treat female sexual dysfunction, particularly female arousal disorder, is an amount sufficient to enhance the patient's ability to achieve or sustain an aroused state.

The term "free drug" refers to solid particles consisting essentially of the compound of structural formula (I), as opposed to the compound intimately embedded in a polymeric coprecipitate.

The term "lubricant" refers to pharmaceutically acceptable agents that are commonly used in the art as lubricants or glidants in the preparation of solid pharmaceutical formulations. Representative lubricants include, but are not limited to, agents such as talc, magnesium stearate, calcium

stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, and stearic acid. Most preferably, the lubricant is magnesium stearate.

The term "solvate" refers one or more molecules of a solute associated with a molecule of a compound, such as the compound of structural formula (I) associated with a molecule of water or acetic acid.

The term "solid oral dosage form" is used in a general sense to refer to solid pharmaceutical products administered orally. Solid oral dosage forms are recognized by those skilled in the art to include such forms as tablets and capsules, for example.

The term "water-soluble diluent" refers to compounds typically used in the formulation of pharmaceuticals to impart bulk for the manufacture of a tablet of practical size. Water-soluble diluents include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "wetting agent" refers to anionic, cationic, and nonionic surfactants. Nonlimiting, representative wetting agents include sodium lauryl sulfate, docusate sodium (i.e., bis(2-ethyl-

hexyl)sodium sulfosuccinate), ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides and ethoxylated derivatives thereof, and diglycerides and ethoxylated derivatives thereof. Preferably the surfactant is sodium lauryl sulfate or a polyoxyethylene sorbitan fatty acid ester, particularly polysorbate 80.

The nomenclature describing particle size is commonly referred to herein as the "d90." A d90 of 40 means that at least 90% of the particles have a particle size less than 40 microns.

As previously stated, the present invention provides pharmaceutical formulations containing the compound of structural formula (I), as disclosed in Daugan U.S. Patent No. 5,859,006, and pharmaceutically acceptable solvates thereof. A preferred solvent suitable to prepare the compound of structural formula (I) includes acetic acid.

Applicants have found that dosage uniformity, stability, and bioavailability are enhanced by formulating (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (i.e., the compound of structural formula (I), also referred to herein as Compound A), as the active compound with a particular combination of pharmaceutical excipients. The formulations of present invention comprise mixtures of the active compound with a water-soluble diluent, a lubricant, a hydrophilic binder, croscarmellose sodium or crospovidone as a disintegrant,

and, optionally, microcrystalline cellulose and/or a wetting agent.

The total amount of active Compound A in the pharmaceutical formulations is about 0.1% to about 45%, preferably about 0.5% to about 10%, by weight of the formulation. In more preferred embodiments, the active compound is present in an amount of about 1% to about 4%, and most preferably, about 2% to about 4%, by weight of the formulation. The compound of structural formula (I) can be made according to established procedures, such as those disclosed in Daugan U.S. Patent No. 5,859,006, incorporated herein by reference.

The particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulations. Thus, the particle size of the compound of structural formula (I) prior to formulation is controlled by milling the raw compound (as a crystal, amorphous precipitate, or mixture thereof) such that at least 90% of the particles have a particle size of less than about 40 microns (d90=40), and preferably less than about 30 microns. More preferably, at least 90% of the particles have a particle size of less than about 25 microns, still more preferably, less than about 15 microns, and most preferably, less than about 10 microns.

Methods for determining the size of particles are well known in the art. The following nonlimiting method disclosed in U.S. Patent No. 4,605,517, incorporated herein by reference, can be employed. In particular, the laser scattering particle size distribution analysis is effected on a

small sample of the reduced material which is suspended in approximately 180 ml of dispersant solution. The sample is added to the dispersant until an acceptable level of laser light obscuration is achieved, at which point the particle size distribution is measured. Prior to sample suspension, a dispersant solution is prepared by preparing a solution of 0.1% SPAN 80 (sorbitan oleate) in cyclohexane which is presaturated with the compound. The dispersant solution is filtered through a 0.2 micron microporous membrane filter to provide the necessary particle-free suspending dispersant. Triplicate measurements are effected as a minimum (a) to produce more reliable measurements, and (b) to check the equivalent sampling of the suspended material. The results are automatically recorded and displayed graphically to give a cumulative % undersize vs. diameter, and a frequency percentage vs. diameter for the sample. From this data, the median equivalent spherical volume diameter value and d90 are derived (90% undersize value) together with the standard deviation of the distribution calculated as above.

A water-soluble diluent is present in the formulation in an amount sufficient to provide adequate bulk to the formulation, and to effect tablet manufacture. A preferred water-soluble diluent is lactose, present in an amount of about 50% to about 85%, and preferably, about 50% to about 75%, by weight.

A hydrophilic binder is provided in an amount sufficient to act as an adhesive to hold Compound A and excipients together in a tablet. A

hydrophilic binder also is present in a powder formulation introduced into a hard gelatin shell. In dry powder formulations, the hydrophilic binder facilitates powder manufacture and handling, and enhances stability of the active compound.

A preferred hydrophilic binder is a cellulose derivative, including, for example, hydroxypropylcellulose and hydroxypropyl methylcellulose. Other hydrophilic cellulose derivatives include, but are not limited to, hydroxyethylcellulose and hydroxybutyl methylcellulose. Another nonlimiting hydrophilic binder is povidone. Preferably, the amount of hydrophilic binder present in the formulation is about 1% to about 5%, by weight of the formulation.

While binders such as povidone provide suitable adhesive characteristics, it has been found that the binder is important with respect to the stability of the β-carboline compound. Hydroxypropylcellulose and hydroxypropyl methylcellulose offer acceptable adhesion, while avoiding the oxidative instability attributed to povidone, and thus are preferred binders.

The croscarmellose sodium and crospovidone promote disintegration of the formulation, and especially a tablet dosage form, after administration and upon contact with water. Croscarmellose sodium and crospovidone are particularly advantageous when used in an amount of about 3% to about 15%, and especially about 3% to about 10%, by weight of the formulation. Croscarmellose sodium, also known as carboxymethylcellulose sodium crosslinked,

is the preferred disintegrant. Crospovidone is crosslinked povidone.

A lubricant is provided in an amount sufficient to reduce die wall friction during compression of the formulation into tablets. Preferably, the lubricant is magnesium stearate, present in an amount of about 0.25% to about 2.0%, by weight of the formulation. A lubricant also facilitates handling of the dry powder form of the formulation.

Microcrystalline cellulose is present at 0 to about 40% by weight in the present compositions. Microcrystalline cellulose can serve multiple functions in the formulation, e.g., a disintegrant and/or a second diluent in addition to the water-soluble diluent.

If desired, wetting agents are provided in an amount sufficient to decrease interfacial tension between drug particles and the dissolving medium (e.g., gastric fluids), and thereby enhance drug dissolution and absorption. Preferably, the surfactant is sodium lauryl sulfate or a polyoxyethylene sorbitan fatty acid ester, particularly polysorbate 80, in an amount of 0% to about 5%, and preferably about 0.1% to about 5%, by weight of the formulation.

Additional optional ingredients, such as coloring or flavoring agents, can be incorporated into the formulation in an amount sufficient to perform their intended function without adversely affecting either the powder formulation or tablets manufactured using the formulation.

In preferred embodiments, the relative percentage of formulation components (by weight) is as follows:

	Quantity (% by weight)
Compound of Structural Formula (I)	1 to 4
Lactose (diluent)	50 to 85
Hydrophilic Binder	1 to 5
Croscarmellose Sodium (disintegrant)	3 to 15
Sodium Lauryl Sulfate (wetting agent)	0 to 5
Microcrystalline Cellulose (diluent/disintegrant)	0 to 40
Magnesium Stearate (lubricant)	0.25 to 2

The formulations of the present invention can be prepared by a variety of techniques recognized in the art. Such techniques include, for example, wet granulation followed by drying, milling and compression into tablets with or without film coating, dry granulation followed by milling, compression into tablets with or without film coating, dry blending followed by compression into tablets, with or with film coating, molded tablets, wet granulation, dried and filled into gelatin capsules, dry blend filled into gelatin capsules, or suspension or solution filled into gelatin capsules. Generally, the compositions have identifying marks which are debossed or imprinted on the surface.

In addition to improved dissolution and *in vivo* absorption, another important physical property is stability. The present invention provides formu-

lations with improved stability over prior formulations.

The specific dose of Compound A administered according to the present invention is determined by the particular circumstances surrounding the case including, for example, the route of administration, the dosage form, the condition of the patient, and the pathological condition being treated. A typical daily dose contains a dosage level of about 1 to about 20 mg/day of the compound of structural formula (I). Preferred daily doses generally are about 1 to about 10 mg/day, particularly about 5 mg or about 10 mg tablets or capsules, administered once per day. The most preferred dosage form is a tablet. Multiple doses can be taken to achieve a total dose of up to 20 mg/day of the compound of structural formula (I). The selection of dose level is decided by the attending physician.

One useful dosage form is a hard capsule comprising a powdered form of the formulation in a hard, soluble shell. In accordance with the present invention, the hard capsules are a solid dosage form in which dry, free-flowing particles of the drug formulation are filled in a hard container or shell comprising a gelatin, a starch, or other capsule materials well known to persons skilled in the art. Gelatin possesses unique properties which make gelatin the primary material for the manufacture of hard capsule shells. Another example of a useful capsule material is potato starch.

Hard capsules provide some advantages over other solid dosage forms, such as tablets. For

example, many patients prefer capsules because capsules are easier to swallow. Thus, capsule forms of a drug often are made available in addition to tablet forms.

A hard capsule has a hard shell completely surrounding the dry formulation. Typically, the dry drug formulation is added to a first section of the capsule, then a second section of the capsule is slipped over an open end of the first section to surround the drug formulation. The size and shape of the hard shell can vary, but typically is cylindrical with rounded ends. The size of the capsule is related to the dose level of the drug encapsulated by the shell, and to the particular drug formulation.

A hard capsule oral dosage form typically is prepared such that the shell ruptures or dissolves to release the enclosed drug formulation within five to ten minutes after ingestion. Manufacture of the hard shell, and the capsules, is performed in accordance with methods well known in the art.

The following formulation examples are illustrative only, and are not intended to limit the scope of the present invention. In particular, the following examples are directed to tablets, but the identical formulations, in a dry free-flowing particulate or powder form, can be used in a hard capsule.

EXAMPLE 1

Lot 1 of Compound A was made using a 12 inch pancake style jet mill fed at a rate of 28 to 30 kg/hour with sufficient grind pressure to produce material having a d90 of 4 microns.

The following formula was used to prepare the finished dosage form, i.e., a tablet providing 10.0 mg of Compound A from Lot 1 material.

Ingredient	Quantity (mg)
Granulation	
Compound A (d90 of 4)	10.0
Lactose Monohydrate	153.8
Lactose Monohydrate (spray dried)	25.0
Hydroxypropyl Cellulose	4.0
Croscarmellose Sodium	9.0
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.7
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.5
Croscarmellose Sodium	7.0
Magnesium Stearate (vegetable)	1.25
Total	250 mg

Purified Water, USP was used in the manufacture of the tablets. The water was removed during processing, and minimal levels remained in the finished product.

The tablets were manufactured using a wet granulation process. A step by step description of the process follows: Compound A and excipients were

security sieved. The selective PDE5 inhibitor (i.e., Compound A) was dry blended with lactose monohydrate (spray dried), hydroxypropyl cellulose, croscarmellulose sodium, and lactose monohydrate. The resulting powder blend was granulated with an aqueous solution of hydroxypropyl cellulose and sodium lauryl sulfate using a Powrex or other suitable high shear granulator. Additional water can be added to reach the desired endpoint. A mill can be used to delump the wet granulation and facilitate drying. The wet granulation was dried using either a fluid bed dryer or a drying oven. After the material was dried, it can be sized to eliminate large agglomerates.

Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate were security sieved and added to the dry sized granules. These excipients and the dry granulation were mixed until uniform, using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process can be separated into two phases: (a) the microcrystalline cellulose, croscarmellose sodium and the dried granulation are added to the mixer and blended, followed by (b) the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation then was compressed into tablets using a rotary compression machine. The core tablets, if desired, can be film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets can be lightly dusted with talc to improve tablet handling characteristics.

The tablets can be filled into plastic containers (30 tablets/container) and accompanied by a package insert describing the safety and efficacy of the compound.

EXAMPLE 2

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 5 mg of Compound A of Lot 1.

Ingredient	Quantity (mg)
Granulation	
Compound A (d90 of 4)	5.00
Lactose Monohydrate	109.655
Lactose Monohydrate (spray dried)	17.50
Hydroxypropyl Cellulose	2.80
Croscarmellose Sodium	6.30
Hydroxypropyl Cellulose (EF)	1.225
Sodium Lauryl Sulfate	0.49
Outside Powders	
Microcrystalline Cellulose (Granular-102)	26.25
Croscarmellose Sodium	4.90
Magnesium Stearate (vegetable)	0.88
Total	175 mg

EXAMPLE 3

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 2.5 mg of Compound A.

Ingredient	Quantity (mg)
Granulation	
Compound A	2.50
Lactose Monohydrate	79.395
Lactose Monohydrate (spray dried)	12.50
Hydroxypropyl Cellulose	2.00
Croscarmellose Sodium	4.50
Hydroxypropyl Cellulose (EF)	0.875
Sodium Lauryl Sulfate	0.35
Outside Powders	
Microcrystalline Cellulose (Granular-102)	18.75
Croscarmellose Sodium	3.5
Magnesium Stearate (vegetable)	0.63
Total	125 mg

EXAMPLE 4

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.0
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Stearic Acid (powder)	3.75
Total	252.5 mg

EXAMPLE 5

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Mannitol	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 6

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Povidone	4.00
Croscarmellose Sodium	9.00
Povidone	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 7

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Povidone	4.00
Croscarmellose Sodium	9.00
Povidone	1.75
Polysorbate 80	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 8

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	157.80
Lactose Monohydrate (spray dried)	25.00
Croscarmellose Sodium	9.00
Hydroxypropyl Methylcellulose	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 9

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Sucrose	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 10

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Sodium Stearyl Fumarate	1.25
Total	250 mg

EXAMPLE 11

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	212.50 mg

EXAMPLE 12

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Crospovidone	27.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	19.50
Crospovidone	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 13

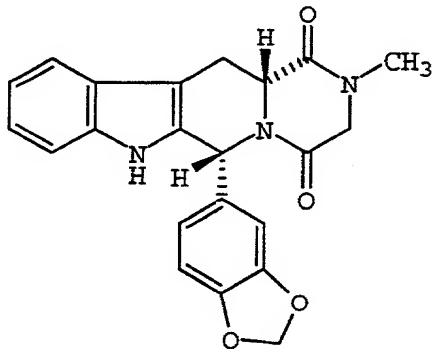
By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	mg/tablet
Granulation	
Compound A	10.00
Lactose Monohydrate	154.50
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate	1.75
Total	**250.0 mg**

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention that is intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug; a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. The formulation of claim 1 further comprising microcrystalline cellulose.

3. The formulation of claim 1 further comprising a wetting agent.

4. The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. The formulation of claim 1 wherein the water-soluble diluent is present in an amount of about 50% to about 85% by weight.

6. The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. The formulation of claim 3 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. The formulation of claim 1 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 40 microns.

18. The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg or about 10 mg per tablet.

25. A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation of any one of claims 1 through 21.

27. The invention as hereinabove described.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/08686 A1

(51) International Patent Classification[7]: A61K 31/495, 9/20, A61P 15/10

(21) International Application Number: PCT/US00/11130

(22) International Filing Date: 26 April 2000 (26.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/146,924 3 August 1999 (03.08.1999) US

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW) , Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) , European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE) , OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/08686 A1

(54) Title: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Formulations containing a PDE5 inhibitor, a water-soluble diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcrystalline cellulose and/or a wetting agent, and their use in treating sexual dysfunction.

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "β-CARBOLINE PHARMACEUTICAL COMPOSITIONS," the specification of which (check one): ☐ is attached hereto; ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11130 on April 26, 2000, and was amended under Article 19 on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

OIPE JC14 APR 29 2002 PATENT & TRADEMARK OFFICE

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(Application Serial Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed ☒ Yes	☐ No
PCT/US00/11130	PCT	26/04/00		
			☐ Yes	☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

(Application Serial Number)	(Day/Month/Year Filed)
60/146,924	03/08/99

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

APPLICABLE RULES AND STATUTES

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and
(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full power of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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